9-27-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004748

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBEJECT: Tebuthiuron
N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-
N,N'-dimethylurea
Tox. Chem. 366AA

FROM: Ray Landolt
Review Section #1
Toxicology Branch/HED (TS-769) 9-27-85

TO: Robert J. Taylor
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

Registrant: Elanco Products Co. May 9, 1985

EPA No. 1471-147 (dry flowable preemergence and postemergence herbicide)
1471-101 (Technical)

Action Requested:

1. Review of a 21-Day dermal toxicity study conducted with the technical formulation (97.8%) identified as EL-103, compound 75503.

2. Request for an exemption from a 21-day dermal toxicity testing for the 85% dry flowable formulation based on "no systemic toxicity at the limit dose (1000 mg/kg) in a 21-day dermal toxicity study", conducted with the technical formulation.

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SH 105501

Recommendation:

The 21 day dermal toxicity study on the technical formulation could be upgraded with additional dosage levels to establish a systemic no-effect level rather than conduct a 21-day dermal study on the 85% use formulation.

21-Day Dermal - Rabbit
Lilly Research Lab. No.. B01484, March 1985, Acc. No. 258052

A. **Procedure**

Two groups of five male and five female 12-16 week old New Zealand White rabbits weighing approximately 2.58 kg were dosed dermally at 0 and 1000 mg/kg, 6 hours per day for 21 consecutive days with the dry form of the technical material (97.8%). The test material was applied to a damp gauze pad that was equivalent in size to 10 percent of each rabbit's body surface area then place on the rabbit's back, covered with an elastic nonocclusive bandage and secured with tape. The animals were fitted with collars and housed individually. Following the 6-hour exposure the dressing was removed and the test areas was rinsed with tap water and dried. Body weights were recorded each week with doses adjusted to changes in body weight. Food consumption was measured daily. Ophthalmic examination, hematology, and clinical chemistry evaluations. were performed initially and at the termination of the study. The animals were observed twice daily for signs of toxicity and for dermal irritation prior to treatment. At the termination of the study all animals were necropsied, organ weights recorded, and tissues collected at necropsy examined microscopically.

B. **Results**

1. Gross Observations
   a. No signs of toxicity, occular effects or deaths were reported.
   b. Slight erythema was observed within three days (2/10), clearing by day 7.
   c. The mean body weight gain and food consumption of the test and control groups were comparable. One female (No. 175731) of the treated group failed to gain weight over the test period which was evident by the decrease in food consumption for this animal.

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2. Clinical Observations
   a. Hematology
      i. A statistically significant increase in the mean corpuscular hemoglobin was observed for the treated females, but comparable to the pretest values.

   b. Chemistry
      i. A statistically significant increase in male glucose values was reported as compared to controls accompanied by an observed decrease in male total bilirubin (22%) and alkaline phosphatase values (22%).

      ii. Male alanine transaminase values were statistically decreased as compared to the controls, but comparable to the pretest control values.

3. Terminal Observations
   a. Organ weights
      i. Increases in ab solute (14-20%) and relative (16-17%) weights of the spleen were observed for both sexes.

      ii. Decrease in female relative adrenal (24%) weights were observed.

   b. No gross pathological changes were observed.

   c. Histopathology
      i. Liver congestion was reported for one female (No. 175841) of the treated group.

      ii. Focal granulomas of the cerebrum and cerebellum were reported for another female (No. 175831) of the treated group that was "probably due to an infectious organism". The incidence of focal granuloma in the central neverous system of rabbits is a common occurrence (Dr. Kasza).

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C. Conculsion

1. Classification of data - Supplementary

2. No observable effect level is less than 1000 mg/kg.
   a. Decreased body weight gain and food consumption were observed for one animal.

   b. Significant increases in male blood glucose levels accompanied by a decrease in bilirubin and alkaline phosphatase values were observed.

   c. Decreased female relative adrenal weights were observed.

   d. Increased absolute and relative spleen weights of both sexes were observed.

   e. Liver congestion was observed for one treated female.

Reviewer's Note: Guidelines recommend that if toxic effects are noted in a single dose study, a full study using three doses may be necessary

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